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10/563,439	01/05/2006	Stephen Robert Wedge	056291-5227	9937

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EXAMINER	
PACKARD, BENJAMIN J	
ART UNIT	PAPER NUMBER
4173	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,439	WEDGE, STEPHEN ROBERT	
	Examiner	Art Unit	
	Benjamin Packard	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *2 and 4-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *(1 sheet)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are:

the terms "ionising" and "tumour" are misspelled throughout the specification. The correct spellings are "ionizing" and "tumor". Examples of the misspelling can be on page 1, lines 4-5, page 3, line 13; the term "deionise" is misspelled at page 17 line 10. The correct spelling is "deionize"; the term "randomised" is misspelled at page 17, line 4. The correct spelling is "randomized".

Appropriate corrections are required.

Claim Objections

Claims 2, 4, and 6 are objected to because of the following informalities: the term "ionising" is misspelled. The correct spelling is "ionizing". Appropriate correction is required.

Claims 5-6 are objected to because of the following informalities: the term "tumour" is misspelled. The correct spelling is "tumor". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating colorectal cancer, does not reasonably provide enablement for "treating cancer". Applicant claims a method for the treatment of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill level:</u>

It is unpredictable whether a drug can be used to treat a patient having cancer. In the case of cancer, it cannot be predicted if a drug will be successful in treating one type of cancer and this unpredictability increases when trying to treat a broad spectrum of cancers. Although many of the tests are functions related to cancers, these functions are not related to all cancers. Furthermore, even testing functions that are related to particular cancers can be misleading because a controlled environment in vitro cannot • predict what will happen in vivo.

a. Anticancer Assays

The unpredictable nature of cancer assays has long been recognized. See, e.g., Gura (Science, vol. 278, pp. 1041-1042 (1997)), which provides an overview of the problems involved with sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile. Since formal screening began in 1955 many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (second paragraph of the article). As noted therein, the "fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." The reasons are many, including basic differences between human patients on the one hand, and animal and cell culture models on the other (third paragraph of the article).

An efficient means of predicting activity with in vivo models remains desirable for compounds with anti-proliferative activity in vitro to this day. See the abstract of Johnson et al., British Journal of Cancer, vol. 84(10), pp. 1424-1431 (2001). As noted at

the bottom of page 1424, the current "drug screening and development scheme remains an empirical one." See also the first paragraph of the "Discussion" section at page 1430 wherein the authors state that "analysis of xenograft versus clinical results illustrates that a histology to histology comparison of these models to activity in the clinic cannot be reliably discerned for these 'empirically' selected compounds acting against non-molecularly characterized tumors."

b. Angiogenesis/Metastasis

Therapies targeted to the common mechanism of angiogenesis have been tried as a means to overcoming the problems arising from the tremendous heterogeneity among different cancer types. Antiangiogenic therapies remain unpredictable, however, and have mainly failed due to numerous factors, including poor correlation between activity in rodent models and therapeutic efficacy in human patients; the tissue and/or tumor specific nature of vasculature; and the lack of a feasible means to monitor antiangiogenic response in patients. Due to these difficulties, additional markers associated with specific pathologies must further be identified, and even when there are no reasonable expectation of therapeutic success can be guaranteed (in part because drug delivery to the ischaemic site can be a major limiting factor, especially given the lack of tools with which to monitor site specific drug availability within the tumor). See Gupta et al., Postgrad. Med. J., vol. 81, pp. 236-242 (2005) at the passage bridging the bottom of the left hand column to the penultimate line on page 239.

As a result of such difficulties, different types of cancers must follow individualized strategies for angiogenesis based treatment. Consequently, most "treatments hold promise but will have to be clinically tested for different kinds and different stages of tumor growth." Gupta et al. at the left hand column of page 240.

2. The breadth of the claims:

The claim is very broad and inclusive of chemotherapy generally.

3. The amount of direction or guidance provided and the presence or absence of working examples:

The specification provides guidance for colorectal cancer only. Applicant provides guidance to treat colorectal carcinoma with AZD2171 (3 mg/kg/day orally, day 0 to day 14), ZD6126 (100 mg/kg/day i.v., day 0 to day 2), or a combination thereof with either "concurrent administration" (AZD2171 day 0 - day 14 combined with ZD6126 day 0 - day 2, where AZD2171 was dosed 2 hours prior to ZD6126) or "sequential administration" (ZD6126 day 0 - day 2 followed by ZD2171 day 3 - day 14).

4. The quantity of experimentation necessary:

Because of the known unpredictability of the artl and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used as an anti-cancer agent for the chemotherapeutic strategies as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement

requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

DETAILED ACTION

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are direct to "the production of an antiangiogenic and/or vascular permeability reducing effect", but fail to disclose what the reducing effect is. As such, one skilled in the art would not understand what is required to practice the method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-14 provide for the use of AZD2171 and ZD6126, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being' indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-6, the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd.App. 1967) and Clinical Products, Ltd. v. Brenner, 255 F. Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 are rejected under 35 USC 103(a) as being unpatentable over US 2003/0055024 ('024) in view of WO 01/74360 ('360) and US 6,420,335 ('335).

Determination of the scope and content of the prior art (MPEP 2141.01)

'024 discloses the use of a vascular-damaging agent (i.e., an antiangiogenic, in particular ZD6126) in the manufacture of a medicament for administration in divided doses, optionally with a pharmaceutically acceptable excipient or carrier (¶ 0017-20), for the use in the production of a vascular-damaging effect in a human (abstract) particularly a method for the treatment of a cancer involving a solid tumor (¶ 0001).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

'024 does not expressly disclose administering together with AZD2171 and/or ionizing radiation.

Finding of prima facie obviousness

'360 discloses 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-l-yl) propoxy) quinazoline (i.e., AZD2171) as a preferred antiangiogenic. (page 16, lines 15-24; page 24, lines 6 and 20).

'335 discloses combination therapy using ionizing radiation and antiangiogenic factors (See claims and Brief Summary).

'024, '335 and '360 are analogous art because they are from the same field of endeavor, treating cancer with the combination of anticancer methods involving antiangiogenic compounds.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to combine the teachings in the references to obtain the invention as claimed.

Rational and Motivation (MPEP 2142.2143)

The suggestion/motivation for doing so would have been to add another antiangiogenic together with ZD6126 ('024 at page 4, ¶ 63 - ¶ 64) along with ionizing

radiation treatment with the expectation to achieve an additive anticancer effect. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In this case, AZD2171 and ZD 6126 are equivalents in that they are both antiangiogenic compounds used to treat certain cancers.

Therefore, it would have been obvious to combine the teachings in each reference to obtain the invention as specified in claim(s).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (/n re Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989);/n re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the i references, especially in the absence of evidence to the contrary.

Claims 1-8 are rejected under 35 USC 103(a) as being unpatentable over US 2003/0055024 ('024) in view of US WO00/47212 ('212) and US 6,420,335 ('335)°

Determination of the scope and content of the prior art (MPEP 2141.01)

'024 discloses the use of a vascular-damaging agent (i.e., an antiangiogenic, in particular ZD6126) in the manufacture of a medicament for administration in divided doses, optionally with a pharmaceutically acceptable excipient or carrier (¶ 0017-20), for the use in the production of a vascular-damaging effect in a human (abstract) particularly a method for the treatment of a cancer involving a solid tumor (¶ 0001).

Ascertainment of the difference between the prior art and the claims (MPEP 2.141.02)

'024 does not expressly disclose administering together with AZD2171 and/or ionizing radiation.

Finding of prima facie obviousness

'212 discloses 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-l-yl) propoxy) quinazoline (i.e., AZD2171) as an antiangiogenic. (claims 1, 9 and 18 and 21-22).

'335 discloses combination therapy using ionizing radiation and antiangiogenic factors (See claims and Brief Summary).

'024, '335 and '212 are analogous art because they are from the same field of endeavor, treating cancer with the combination of anticancer methods involving antiangiogenic compounds.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to combine the teachings in the references to obtain the invention as G claimed.

Rational and Motivation (MPEP 2142-2143)

The suggestion/motivation for doing so would have been to add another antiangiogenic together with ZD6126 ('024 at page 4, ¶ 63 - ¶ 64) along with ionizing radiation treatment with the expectation to achieve an additive anticancer effect. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In this case, AZD2171 and ZD 6126 are equivalents in that they are both antiangiogenic compounds used to treat certain cancers.

Therefore, it would have been obvious to combine the teachings in each reference to obtain the invention as specified in claim(s).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (In re Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); In re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one

of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set . forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin et al (WO 01/32651) in view Magne et al. (British Journal of Cancer, vol 86, No 5, 4 march 2002, pp 819-827).

Claims 1-6 are drawn to a method for the treatment of cancer and a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, which comprises administering ZD6474 and ZD1839, optionally with an effective amount of ion!zing radiation. Claims 7 and 8 are drawn to a pharmaceutical composition and kit comprising ZD6474 and ZD1839.

Hennequin et al discloses a method for the treatment of cancer, solid tumors in particular (p.28, lines 11-17), and a method for the production of an antiangiogenic

and/or vascular permeability reducing effect in a warm-blooded animal (p. 26, lines 10-14), which comprises administering a compound of formula I (p. 3). ZD6474 is specifically identified as a compound of Formula I (claim 8). Hennequin et al further teaches that this treatment may additionally include radiotherapy administered simultaneously, sequentially or separately (p. 26, lines 22-30).

Hennequin et al does not teach this method of treatment further comprising the administration of ZD1839.

Magne et al teaches that ZD1839 (Iressa) enhances the growth inhibitory effect of other cytotoxic drugs (p. 825, second column). Magni et al further teaches that ZD1839 is a strong radiosensitizer as well as chemosensitizer (p. 826, first column).

Therefore it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add the step of administrating ZD1839 to the method of treatment described in Hennequin et al, because of its known chemosenstizing and radiosensitizing activity, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

Furthermore, combining ZD6474 and ZD1839 into a pharmaceutical composition or kit would have been obvious to one of ordinary skill in the art at the time of the invention, since they were both known chemotherapeutic agents. Applicant is reminded of in re Kerkhoven, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose .... ['I']he idea

of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)

The addition of a pharmaceutically acceptable carrier or excipient to the aforementioned pharmaceutical composition would have been obvious to one of ordinary skill in the art at the time of the invention to allow for effective administration to the patient and delivery to the targeted tissue.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-14 of copending Applications No. 10/563,440, 10/523,838. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-R 9-4:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

27 November 2007
BP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614